AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions and listings of claims in the application:

1-23. (Cancelled).

24. (Previously Presented): A DNA gene inactivation construct for homologous recombination in the genome of a mammalian cell, comprising at least 100 bp of a sequence homologous with a gene locus of a subunit of an MHC antigen flanking a sequence encoding a selectable marker gene capable of expression in a mammalian cell, wherein the sequence encoding a selectable marker gene is downstream from a sequence encoding a leader sequence and is fused in frame to a transmembrane coding region of the subunit of the MHC antigen, wherein upon homologous recombination, said gene locus is inactivated, and wherein, as a result of homologous recombination, at least one functional MHC antigen is not expressed.

25. (Previously Presented): A DNA construct according to claim 24, wherein said MHC antigen is selected from the group consisting of Class I and Class II antigens.

26. (Previously Presented): A DNA construct according to claim 24, wherein said subunit of an MHC antigen is β_2-microglobulin.

27. (Previously Presented): A DNA construct according to claim 24, wherein said selectable marker gene is an antibiotic resistance gene.

28. (Previously Presented): A DNA construct according to claim 27, wherein said selectable marker gene is selected from the group consisting of the Neo resistance gene and the hygromycin resistance gene.

29. (Previously Presented): A DNA construct, comprising DNA encoding in the 5' to 3' direction,

a region of homology to a target gene,

a foreign promoter/enhancer joined to a first epitope that binds to a ligand for detection,

a selectable marker gene, and

a second region of homology to said target gene,

said target gene encoding a gene product having a second epitope, and said target gene being selected from the group consisting of a gene encoding a subunit of an MHC antigen and a gene encoding a protein that upregulates expression of MHC antigens,

wherein, upon homologous recombination of said DNA construct into a genome, a recombinant, secreted fusion protein comprising said first epitope that binds to a ligand for detection and said second epitope is expressed in targeted cells, and

wherein, as a result of homologous recombination, at least one functional MHC antigen or protein associated with expression of MHC antigens is not expressed.

30. (Previously Presented): A DNA construct according to claim 29, wherein said first epitope is CD4.

31. (Previously Presented): A DNA construct comprising DNA encoding a transcriptionally and translationally impaired positive selectable marker gene fused in frame to the transmembrane coding region of an integral membrane protein receptor for a cytokine that upregulates the expression of MHC antigen;

wherein the expression product of said DNA is a fusion protein comprising a functional selectable marker expressed on the cytoplasmic side of said membrane.

32. (Previously Presented): A DNA construct according to claim 31, wherein said integral membrane protein is IFNγR and said selectable marker gene is the neomycin resistance gene.

33. (Previously Presented): A DNA construct according to claim 29, wherein said target gene is selected from the group consisting of genes encoding MHC antigen subunits, T cell receptor subunits, interferon receptors, neurotransmitter receptors, growth factor receptors, IL-1R, TAP 1, TAP 2, β_2-microglobulin, proteosome subunits and colony stimulating factor receptors.

34. (Previously Presented): A DNA construct according to claim 33, wherein said target gene encodes β_2-microglobulin.

35. (Previously Presented): A DNA construct according to claim 31, wherein said integral membrane protein is selected from the group consisting of interferon receptors, IL-1R, and colony stimulating factor receptors.

36. (Previously Presented): A DNA construct comprising DNA encoding a transcriptionally and tanslationally impaired positive selectable marker gene fused downstream and in frame to the transmembrane coding region of an integral membrane protein that upregulates MHC antigen expression, wherein the expression product of said DNA construct is a fusion protein comprising a functional, selectable marker.

37. (Previously Presented): The DNA construct of claim 36, wherein said integral membrane protein is selected from the group consisting of MHC antigen subunits T cell receptor subunits, neurotransmitter receptors, growth factor receptors, TAP1, TAP2, β_2-microglobulin and proteosome subunits.

38. (Previously Presented): A DNA gene inactivation construct for homologous recombination in the genome of a mammalian cell, comprising a first sequence homologous with a gene locus present in the genome of the mammalian cell, having a length of at least 150 base pairs, and flanking a sequence encoding a selectable marker gene capable of expression in the mammalian cell, wherein the sequence encoding the

selectable marker gene is downstream from a sequence encoding a leader sequence and is fused in frame to a coding sequence encoding an expression product, wherein the leader sequence comprises a second sequence homologous with the gene locus present in the genome of the mammalian cell and having a length of at least 150 base pairs, wherein upon homologous recombination said gene locus is inactivated, and wherein, as a result of homologous recombination, at least one functional expression product encoded by said gene locus is not expressed.

39. (Previously Presented): A DNA construct according to claim 38, wherein said selectable marker gene is the Neo resistance gene.

40. (Previously Presented): A DNA construct according to claim 38, wherein said gene locus present in the genome of the mammalian cell is a receptor, and the coding sequence encoding an expression product encodes part or all of the receptor or a modified version of the receptor.

41. (Previously Presented): A DNA construct according to claim 40, wherein the receptor is a receptor for an infectious or toxic agent.

42. (Previously Presented): A DNA construct according to claim 40, wherein the receptor is a retinoic acid receptor.

43. (Previously Presented): A DNA construct according to claim 40, wherein the receptor is a 3-β adrenergic receptor.

44. (Previously Presented): A DNA construct according to claim 40, wherein the receptor is an HIV receptor.

45. (Previously Presented): A DNA gene inactivation construct for homologous recombination in the genome of a mammalian cell having a recipient DNA sequence, wherein said recipient DNA sequence comprises complementing DNA comprising a first nucleotide sequence and a second nucleotide sequence downstream of said first nucleotide sequence, wherein the DNA gene inactivation construct comprises:

(1) a third nucleotide sequence homologous to said first nucleotide sequence;

(2) a fourth nucleotide sequence homologous to said second nucleotide sequence; and

(3) a DNA sequence heterologous with respect to said recipient DNA sequence, wherein said heterologous DNA sequence is between said third and said fourth nucleotide sequences and said heterologous DNA sequence comprises a first insertion DNA sequence and a second insertion DNA sequence, wherein said first insertion DNA sequence comprises a first coding sequence that encodes a first product that does not confer resistance to a selection agent involved in the selection of transformants, and said second insertion DNA sequence comprises a second coding sequence that encodes a second product

that confers resistance to a selection agent involved in the selection of transformants, wherein upon insertion of said heterologous DNA sequence between said first and said second nucleotide sequences in said recipient DNA sequence by homologous recombination with said third and said fourth nucleotide sequences, to thereby provide a mammalian cell containing the recombinant DNA sequence, said second coding sequence is operably linked to a regulatory sequence allowing the expression of said second product in said mammalian cell.

46. (Previously Presented): A DNA construct according to claim 45, wherein said selection agent is neomycin.

47. (Previously Presented): A DNA construct according to claim 45, wherein said recipient DNA sequence in the genome of a mammalian cell is a receptor, and wherein the first product that does not confer resistance to a selection agent involved in the selection of transformants is part or all of the receptor or a modified version of the receptor.

48. (Previously Presented): A DNA construct according to claim 47, wherein the receptor is a receptor for an infectious or toxic agent.

49. (Previously Presented): A DNA construct according to claim 47, wherein the receptor is a retinoic acid receptor.

50. (Previously Presented): A DNA construct according to claim 47, wherein the receptor is a 3-β adrenergic receptor.

51. (Previously Presented): A DNA construct according to claim 47, wherein the receptor is an HIV receptor.

52. (Previously Presented): A DNA construct, comprising DNA encoding in the 5' to 3' direction,

a region of homology to a target gene,

a foreign promoter/enhancer joined to a first coding sequence that encodes a first gene product,

a selectable marker gene, and

a second region of homology to said target gene,

said target gene comprising a second coding sequence encoding a second gene product,

wherein, upon homologous recombination of said DNA construct into a genome, a recombinant, fusion protein comprising said first gene product and part or all of said second gene product is expressed in targeted cells, and wherein, as a result of homologous recombination, at least one functional copy of the target gene is not expressed.

53. (Previously Presented): A DNA construct according to claim 52, wherein the selectable marker gene encodes resistance to neomycin.

54. (Previously Presented): A DNA construct according to claim 52, wherein the first gene product is part or all of a receptor.

55. (Previously Presented): A DNA construct according to claim 54, wherein the receptor is a receptor for an infectious or toxic agent.

56. (Previously Presented): A DNA construct according to claim 54, wherein the receptor is a retinoic acid receptor.

57. (Previously Presented): A DNA construct according to claim 54, wherein the receptor is a 3-β adrenergic receptor.

58. (Previously Presented): A DNA construct according to claim 54, wherein the receptor is an HIV receptor.

59. (Previously Presented): A DNA construct according to claim 52, wherein the first gene product is part or all of an interferon.

60. (Previously Presented): A DNA construct according to claim 52, wherein the first gene product is part or all of an interleukin.

61. (Previously Presented): A DNA construct according to claim 52, wherein the target gene is part or all of a receptor.

62. (Previously Presented): A DNA construct according to claim 61, wherein the receptor is a receptor for an infectious or toxic agent.

63. (Previously Presented): A DNA construct according to claim 61, wherein the receptor is a retinoic acid receptor.

64. (Previously Presented): A DNA construct according to claim 61, wherein the receptor is a 3-β adrenergic receptor.

65. (Previously Presented): A DNA construct according to claim 61, wherein the receptor is an HIV receptor.

66. (Previously Presented): A DNA construct according to claim 52, wherein the target gene is part or all of an interferon.

67. (Previously Presented): A DNA construct according to claim 52, wherein the target gene is part or all of an interleukin.

68. (Previously Presented): A DNA construct comprising a first DNA sequence and a second DNA sequence, wherein said first DNA sequence comprises a first coding sequence that encodes a first gene product that does not confer resistance to a selection agent involved in the selection of transformants, and said second DNA sequence comprises a second coding sequence that encodes a second gene product that confers resistance to a selection agent involved in the selection of transformants, wherein the second DNA sequence is downstream of the first DNA sequence, wherein the expression product of said DNA construct comprises the second product that confers resistance to a selection agent involved in the selection of transformants, in functional form.

69. (Previously Presented): A DNA construct according to claim 68, wherein the selective agent is neomycin.

70. (Previously Presented): A DNA construct according to claim 68, wherein the expression product of said DNA construct localizes in the cytoplasm when expressed in a mammalian cell.

71. (Previously Presented): A DNA construct according to claim 68, wherein the first gene product is part or all of a receptor.

72. (Previously Presented): A DNA construct according to claim 71, wherein the receptor is a receptor for an infectious or toxic agent.

73. (Previously Presented): A DNA construct according to claim 71, wherein the receptor is a retinoic acid receptor.

74. (Previously Presented): A DNA construct according to claim 71, wherein the receptor is a 3-β adrenergic receptor.

75. (Previously Presented): A DNA construct according to claim 71, wherein the receptor is an HIV receptor.

76. (Previously Presented): A DNA construct according to claim 68, wherein the first gene product is part or all of an interferon.

77. (Previously Presented): A DNA construct according to claim 68, wherein the first gene product is part or all of an interleukin.

78. (Previously Presented): A DNA gene inactivation construct for homologous recombination in the genome of a mammalian cell, comprising a first sequence homologous with a gene locus present in the genome of the mammalian cell, having a length of at least 150 base pairs, and flanking a sequence encoding a selectable marker gene capable of expression in the mammalian cell, wherein the sequence encoding the selectable marker gene is downstream from a sequence encoding a leader sequence and is fused in frame to a coding sequence encoding an expression product, wherein

the expression product of said DNA construct localizes to the cytoplasm when expressed in a mammalian cell, wherein the leader sequence comprises a second sequence homologous with the gene locus present in the genome of the mammalian cell and having a length of at least 150 base pairs, wherein upon homologous recombination said gene locus is inactivated, and wherein, as a result of homologous recombination, at least one functional expression product encoded by said gene locus is not expressed.

79. (New): A method for modifying a target DNA sequence in a mouse embryonic stem cell comprising:

(a) introducing in vitro a targeting DNA sequence into the mouse embryonic stem cell derived from an inbred mouse strain, said targeting DNA sequence is isolated from said inbred mouse strain; and

(b) isolating in vitro the mouse embryonic stem cell whose target DNA sequence has been modified by incorporation of said targeting DNA sequence into a nonselectable gene of the target sequence.

80. (New): The method of claim 79, wherein said inbred mouse strain is 129.

81. (New): The method of claim 79, wherein said inbred mouse strain is BALB/c.

82. (New): The method of claim 79, wherein said mouse embryonic stem cell is derived from a substrain of said inbred mouse strain.

83. (New): The method of claim 79, wherein said targeting DNA sequence is isolated from a substrain of said inbred mouse strain.

84. (New): The method of claim 79, wherein said mouse embryonic stem cell is derived from a first substrain of said inbred mouse strain and wherein said targeting DNA sequence is isolated from a second substrain of said inbred mouse strain.

85. (New): The method of claim 84, wherein said first substrain and said second substrain are the same substrain.

86. (New): The method of claim 79, wherein said targeting DNA sequence, except for desired sequence modifications, is at least about 99.5% identical with said target DNA sequence in the mouse embryonic stem cell.

87. (New): The method of claim 79, wherein said targeting DNA sequence, except for desired sequence modifications, is at least about 99.9% identical with said target DNA sequence in the mouse embryonic stem cell.

88. (New): The method of claim 79, wherein said targeting DNA sequence contains a selectable marker gene.

89. (New): The method of claim 88, wherein said selectable marker gene is a gene conferring resistance to a compound inhibitory to cell growth.

90. (New): The method of claim 88, wherein said selectable marker gene is a gene conferring the ability to grow on a selected substrate.

91. (New): The method of claim 88, wherein said selectable marker gene is a neomycin resistance gene.

92. (New): The method of claim 88, wherein said selectable marker gene lacks its own promoter.

93. (New): The method of claim 88, wherein said selectable marker gene has no poly(A) sequence.

94. (New): The method of claim 88, wherein said selectable marker gene is placed in an intron.

95. (New): The method of claim 79, wherein said target DNA sequence has been modified by a replacement-type event.

96. (New): The method of claim 79, wherein said target DNA sequence has been modified by an insertion-type event.

97. (New): The method of claim 79, wherein said targeting DNA sequence is part of a DNA delivery molecule which contains additional DNA sequence flanking the targeting DNA sequence.

98. (New): The method of claim 97, wherein said additional DNA sequence contains a selectable marker.

99. (New): The method of claim 79, wherein said targeting DNA sequence, except for desired sequence modifications, is at least about 300 base pairs.

100. (New): The method of claim 79, wherein said targeting DNA sequence, except for desired sequence modifications, is at least about 1000 base pairs.

101. (New): The method of claim 79, wherein said targeting DNA sequence is introduced into said mouse embryonic stem cell by a method selected from the group consisting of microinjection, electroporation, calcium phosphate precipitation, liposome fusion, and transfection using a virus or a viral particle.